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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,504	04/13/2005	John J. Renger	21245YP	9078

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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,504	RENGER ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *13 April 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the 371 of PCT/US03/32892 filed October 15, 2003. Amended claims 33-50 are being examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for some T-type calcium channel antagonists, namely, compounds A-D, does not reasonably provide enablement for enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia with any T-type calcium channel antagonist as set forth in the instant claims. The specification does not provide sufficient information that all T-type calcium channel antagonists are capable of enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia. Thus, the term "T-type calcium channel antagonists" is very broad as cited in claims 33-50.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention

commensurate in scope with these claims. The specification does not provide sufficient information that all T-type calcium channel antagonists are capable of enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia with the administration of a T-type calcium channel antagonists as described in claims 33-50. The nature of the invention is complex in that it encompasses the treatment said ailments using a wide array of compounds encompassed by the term "T-type calcium channel antagonists".

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass methods of enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia by administering a wide array of compounds encompassed the term "T-type calcium channel antagonists". There are countless possible compounds encompassed by "T-type calcium channel antagonists" for the treatments claimed. The general definition "T-type calcium channel antagonists" used in the claims of the present application does not clearly define any chemical compound and is not known in the art to which it pertains. If there is support for the specific T-type calcium channel antagonists, the claims must be limited as such. The claims are therefore much broader than the enabling disclosure.

(3). Guidance of the Specification:

The guidance given by the specification as to how effective the disclosed T-type calcium channel antagonists are at treating the desired ailments is limited, in particular there are no structures provided for compounds A-C in the table on page 17 of the specification. Additionally, there is no data on how effective these compounds are at treating the desired ailments. Further, there is no selectivity data on compound A.

(4). Working Examples:

Applicant provides an example of a preclinical study on the effects of a T-type calcium channel antagonist on sleep (compound A). There is a second clinical study

involving T-type calcium channel antagonists involving healthy young adults, but it is not clear which compounds were tested.

(5). State of the Art:

The most pertinent art that the Examiner is aware involves mibefradil (*AJH*, 1998), a selective T-type calcium channel antagonist. Mibefradil increases coronary blood flow, lowers peripheral resistance, blood pressure, and heart rate, but does not decrease cardiac contractility or stimulate the neuroendocrine system (page 97S).

(6). Nature and predictability of the invention

The nature of the invention is directed towards medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound as encompassed by "T-type calcium channel antagonists", the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test

the combination in the model system to determine whether or not the combination is effective for enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding sleep ailments with any T-type calcium channel antagonists, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to enhance the quality of sleep, augment sleep maintenance and treat insomnia by administration of one of the T-type calcium channel antagonists as set forth in the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, methods of enhancing the quality of sleep, augmenting sleep maintenance and treating insomnia by administering T-type calcium channel antagonists of the claims is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snutch (WO 01/02561 A2).

Snutch teaches T-type calcium channel encoding sequences, expression of these sequences, and methods to screen for compounds which antagonize calcium channel activity (page 1, lines 4-6).

Snutch further teaches the resulting identified compounds are useful in treating conditions where undesirable T-type calcium channel activity is present. These conditions include epilepsy, sleep disorders, mood disorders, cardiac hypertrophy and hypertension, among others. In addition, antisense and triplex nucleotide sequences can be designed to inhibit the production of T-type calcium channels (page 5, lines 8-11).

Snutch does not specifically teach the nature of the sleep disorders (i.e. insomnia).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used the calcium antagonists taught by Snutch for sleep disorders to also have used them as a method for treating insomnia which inherently enhances the quality of sleep and augments sleep maintenance. Insomnia is a species of the sleeping disorder genus, therefore it would have been obvious to have applied the antagonists for this purpose.

Claims 37 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snutch (WO 01/02561 A2) as applied to claims 33-36 above and in further view of Massie (*American Journal of Hypertension*, 1998).

Snutch is discussed above.

Snutch does not teach a T-type calcium channel antagonist that is selective for the T-type calcium channel and the associated binding (ie, IC50).

Massie teaches that in contrast to all calcium channel antagonists, which block the L-type calcium channels, mibefradil selectively blocks T-type calcium channels (page 97S, column 1, lines 1-3).

Massie teaches Mibefradil increases coronary bloodflow, lowers peripheral resistance, blood pressure, and heart rate, but does not decrease cardiac contractility or stimulate the neuroendocrine system (page 97S, column 1, line 9).

Furthermore Massie teaches mibefradil has a very favorable pharmacokinetic profile. Absorption after an oral dose is rapid and unaffected by food.

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the teachings of Snutch as discussed above for treating sleep disorders with T-type calcium channel antagonists using the T-type calcium channel antagonist taught by Massie. One would be motivated to use mibefradil because it possesses characteristics that would helpful in treat sleeping ailments including lowering peripheral resistance, blood pressure, and heart rate.

Claims 41 and 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snutch (WO 01/02561 A2) as applied to claims 33-36 above and in further view of Santi (*Journal Neuroscience*, 2002).

Snutch is discussed above.

Snutch does not discuss the selectivity and binding of the T-type calcium channel antagonists as it pertains to the three calcium channel subtypes (α_{1G}, α_{1H}, and α_{1I}).

Santi teaches the inhibitory effects of the neuroleptic agents pimozide, penfluridol, haloperidol, and flunarizine on three exogenously expressed neuronal T-type calcium channels. The results demonstrate that the diphenylbutylpiperidines (DPBP) class of neuroleptics are high-affinity T-type Ca channel blockers and suggest that Ca channel blockers may represent a significant contribution to the clinical efficacy of these agents (page 397, column 1, first full paragraph).

Santi further teaches the effect of two DPBPs, penfluridol and pimozide (Fig. 1*A,B*), on exogenously expressed α_{1G}, α_{1H}, and α_{1I} T-type Ca channels from rat brain (Fig. 2). Penfluridol and pimozide were not subtype-selective because both of these agents blocked the three neuronal T-type Ca channels to similar extents (Fig. 2, Table 1). A detailed analysis of the concentration–response relations of pimozide and penfluridol with the three T-type Ca channels revealed a similar range of IC50 values in the case of pimozide (34.6, 53.5, and 30.4 nM for α_{1G}, α_{1H}, and α_{1I}, respectively) and IC50 values equal to 93.1, 64.1, and 71.6 nM for α_{1G}, α_{1H}, and α_{1I}, respectively, for penfluridol (page 398, Fig. 2 insert).

Furthermore Santi teaches, flunarizine has been described as the most potent organic blocker of hypothalamic T-type Ca channels. Unlike the other neuroleptics studied, flunarizine displayed a preferential block of α_{1G}, α_{1I} (*K*d = 0.53 and 0.84 μM, respectively) (Table 1) compared with α_{1H} (*K*d = 3.6 μM) (Table 1).

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have to have employed the teachings of Snutch as discussed above for treating sleep disorders with T-type calcium channel antagonists using the T-type calcium channel antagonist taught by Santi. One would be motivated to use said drugs because they are neuroleptics and have the ability to alleviate the symptoms of CNS disorders such as insomnia (http://www.merck.com/mmpe/sec16/ch215/ch215c.html).

Conclusion

Claims 33-50 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

SJ

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER